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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,537	12/15/1999	JOHN C. ROYER	4216.260-US	3928

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/461,537	Applicant(s) ROYER ET AL.	
	Examiner Maria Marovich	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Attachment* .

DETAILED ACTION

Claims 20-23 are pending in the application.
This Office action is in response to the amendment and the Terminal Disclaimer filed ??.

Response to Amendment

Applicants perfect a claim benefit of priority of Application No. 08/816915 filed on March 13, 1997 thus the effective date accorded to the present application is June 30, 1994

Objections to sequence compliance of 37 CFR 1.821 through 1.825 have been withdrawn due to Applicants submission of remarks regarding procedures of CFR 1.821 (e) in which the identical computer readable form from 08/816,915 is to be used in the instant application.

Objection to claim 20 has been withdrawn in light of corrections to now claim 24.

The rejection of claims 20-22 under the judicially created doctrine of obviousness-type double patenting has been withdrawn in light of Applicant's submission of a proper Terminal Disclaimer.

The rejection of claims 20-22 under USC 102 (e) has been withdrawn in light of perfected claim of benefit of copending, parent application 08/816,915.

The rejection of claims 20-22 under USC 102 (a) has been withdrawn in light of perfected claim of benefit of copending, parent application 08/816,915.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23-25 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of cells deposited at ATCC under deposit number 20334, does not reasonably provide enablement for the use of recombinant host cell having the identifying characteristics of a non-toxic, non-toxigenic, non-pathogenic *Fusarium venenatum* host cell. . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Unpredictability of the art. This invention recites a method for the production of proteins by use of *Fusarium venenatum* host cells. The unpredictability of the art is high. Few filamentous fungal host cells are used for protein production and fewer non-toxin producing fungi for this purpose have been identified or developed. This invention specifically recites a recombinant host cell for protein production described as "recombinant host cells having the identifying

characteristics of a non-toxic, non-toxigenic and non-pathogenic *Fusarium venenatum* of the section discolor". Correct "identifying characteristics" for the assignation of said host cells did not exist at the time of invention. The *Fusarium* cells described in the specification, commercially called quorn, were deposited at ATCC with a deposit number of 20334. Quorn was miss-identified and published as such in the ATCC catalog and in the literature as *Fusarium graminearum*. In 1998, O'Donnell **et al** following molecular phylogenetics, morphological and mycotoxin analyses and Yoder **et al** utilizing rapid amplified polymorphic DNA PCR in combination with cultural characterization on minimal media correctly identified these cells as *Fusarium venenatum*. However, we are taught in the specification (and prior art) to classify the host cells based solely on morphological and cultural characteristics.

2) State of the art. Commercial protein production with filamentous fungi was not a high art at the time of invention. Due to the production of undesired toxins- F2 (mycotoxins) and T2 (tricothecenes)- by *Fusarium*, this technique had historically and routinely not utilized these organisms for commercial protein expression. *Fusarium* isolates known as quorn or ATCC 20334 were identified in the early 1970's. This strain was correctly characterized in 1998, which leaves the impression that classification schemes at the time of invention were not completely developed. Quorn was routinely used as an edible protein source due to the lack of toxins produced by ATCC 20334 cells. Other strains and/or species of fungi that were non-toxic, non-toxigenic and non-pathogenic for commercial production of proteins were unidentified at the time of invention.

3) Number of working examples. Extensive working examples utilizing ATCC 20334 cells for transformation and expression from CAREZYME, LIPOLASE and trypsin protease expressing vectors are provided.

4) Amount of guidance provided by applicants. The specification is silent with respect to what identifying characteristics enable correct identification of *Fusarium venenatum*. Colony morphology of *Fusarium graminearum* on PDA are specifically provided which ultimately are not sufficient for *Fusarium venenatum*. As we are taught in Yoder **et al** morphological characteristics are best discernible between strains by growth on minimal media. Cultural characteristics recited in the specification most closely resemble *Fusarium graminearum* and not *venenatum*. Required techniques for the proper execution of identifying *Fusarium venenatum* as well as critical primers and unique cultural details are not provided in the specification. Therefore, no disclosure for a critical aspect of the invention, host cells having the identifying characteristics of a non-toxic, non-toxigenic, non-pathogenic *Fusarium venenatum* host cell is provided. For the implementation of the specific aspects of the invention namely transformation and expression of heterologous nucleic acid sequences, the specification provides guidance for the implementation of this invention with ATCC 20334 cells. We are taught optimal pre-protrypsin gene expression, CAREZYME, LIPOLASE expression in ATCC 20334. In a Declaration filed 12/15/99 by Wendy Yoder (previously addressed in full in the first office action), we are further taught that two *Fusarium venenatum*, strains ATCC 60879 and BPA 64537, provide excellent sources of recombinant host cells due to their transformation efficiency and protein production capability. It is unknown whether ATCC 60879 complies with other requirements for this invention such as non-toxicity and non-pathogenicity.

5) Nature of invention. The invention recites a method for heterologous protein production from recombinant *Fusarium venenatum*. This invention requires a combination of molecular cloning, fungal growth, protein chemistry, and biochemistry techniques. As well, taxonomic classification is required for this invention as the nature of the cells for heterologous protein production must be non-toxic, non-toxigenic and non-pathogenic *Fusarium venenatum*.

6) Level of skill in the art. The level of skill in the art covering many aspects of this invention was high at the time of invention. Using *Fusarium venenatum* for protein expression requires the generation of nucleic acids sequences that contain the gene of interest as well as regulatory sequences- routine components of molecular biology and protein expression protocols for decades. Gene cloning technology unique to filamentous fungi was readily being developed several years prior to invention including cloning vectors, mutant strains and selectable markers. Transformation and fermentation of *Fusarium* were standard fungal growth culture technique readily accomplished by those of ordinary skill in the art. Assays for protein expression were easily accomplished by one of skill in the art. Isolation of proteins from fungal sources was being developed concurrent with the invention but appeared to be advanced enough for proper execution.

7) Scope of the invention. This invention has broad scope in that it recites a general method for high yield production of proteins utilizing a recombinant host cell with the identifying characteristics of a non-toxic, non-toxigenic and non-pathogenic *Fusarium venenatum*. The method claim is broad in that it recites any such host cell comprising any desired gene linked to any desired promoter.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention.

Claim 23-25 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim reads on a genus of cells (recombinant host cells having the identifying characteristics of a non-toxic, non-toxigenic and non-pathogenic *Fusarium venenatum* of the section discolor) and methods of using these cells for the production of recombinant proteins. The written description requirement for genus claims may be satisfied through sufficient description of a relevant a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics such as structure or other physical and/or chemical properties, by functional characteristics couple with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, applicants present as relevant identifying characteristics, colony morphology of (ATCC 20334) *Fusarium graminearum* on PDA. However, this characteristic is not sufficient for *Fusarium venenatum*. In the Yoder declaration, we are taught two additional examples, strains ATCC 60879 and BBA 64357. Neither BBA 64357 nor ATCC 60879 provide adequate examples of said recombinant

host because the non-pathogenic, non-toxigenic nature of ATCC 60879 is unknown and because it is unclear when BBA 64537 was isolated. It must be considered that any recombinant host cell must be empirically determined. It must be considered that the one disclosed example (ATCC 20334) is not a representative number of species to show applicants were in possession of the claimed genus. It must be assumed that the skilled artisan would not conclude that applicant was in possession of claimed genus.

The *Fusarium venenatum* of the invention were apparently deposited by others, their availability in an unrestricted form for the life of a patent issued on the instant application cannot be ensured. Applicants must therefore deposit the specific *Fusarium venenatum* recited in the claims and thus satisfy a deposit requirement under 37 CFR 1.801-1.809 (see enclosed Suggestion for deposit of biological material).

Response to Arguments

On pages 4-6, Applicant traverses the rejections under 35 U.S.C. 112, first paragraph by reciting Nirenberg and Dr.Yoder's Declaration of April 19, 2000 as teachings that enable the skilled artisan to practice the full scope of the claimed invention. Applicant contends that while the designation of *Fusarium venenatum* was initially misidentified, its inherent properties and features existed at the time of invention and that taxonomic classification of other *Fusarium* species was routinely and successfully accomplished. Furthermore, the misidentification of one strain does not mean that species and/or strain designation based upon cultural and morphological characteristics is not reliable.

The rejection of the instant application under 35 U.S.C. 112, first paragraph stands as rejected as containing subject matter not described in the specification in such a way as to either

enable one of skill in the art to use the invention commensurate in scope with these claims or to reasonably convey that the inventor(s) had possession of the claimed invention (Written Description). The claimed invention is drawn to methods of utilizing a recombinant host cell line for heterologous protein expression; the recombinant cells "having the identifying characteristics of a non-toxic, non-toxigenic, non-pathogenic *Fusarium venenatum* of the section Discolor".

Examiner concurs with applicant that the misidentification of one species is no indication that all classification schemes are to be distrusted. However since the misidentified species was *Fusarium venenatum*, the implication is that the inventor was neither in possession of these "identifying characteristics" nor was one of skill in the art enabled to use the invention due to the lack of guidance on this topic. Criteria given for the cultural and morphological identification, the only such identifying characteristic taught in the specification, provided for the identification of *Fusarium graminearum*. Other criteria used to accurately identify specifically *Fusarium venenatum* of the section Discolor were not found in the prior art until 1998. The existence of at least BBA 64537, a non-toxic, non-toxigenic, non-pathogenic *Fusarium venenatum,* is acknowledged (ATCC 60879 at this point does not appear to meet these criteria). The existence of this strain provides another source of heterologous protein production but does not in itself enable the instant application as there is no evidence that these strains were identified at the time of application. Information on BBA 64537 was not available through the literature until 1998 and to this date only oblique references to ATCC 60879 are found. Therefore, the level of skill of one in the art **may** have been high enough for the correct identification of *Fusarium venenatum* but the identifying characteristics required to do so did not exist at the time of invention.

Applicants amendments to the application no longer make dealing with the issue of telemorphs and synonyms an issue.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucell, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and 1 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

April 18, 2002

DAVID GUZO
PRIMARY EXAMINER

file copy

ATTACHMENT

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready availability thereto by the public if a patent is granted. The depository is to be identified by name and address (See 37 CFR 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent (See 37 CFR 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 USC 122 (See 37 CFR 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 CFR 1.806.

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, date of deposit and the complete taxonomic description.